IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Fredman, Jeffrey Norman
Kevin P. BAKER, et al.	)	Art Unit: 1637
Application Serial No. 10/015,387	)	Confirmation No: 9861
Filed: December 12, 2001	)	Attorney's Docket No. 39780-2830 P1C54
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	)	**Customer No. 35489**

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPELLANTS' REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On January 18, 2005, the Examiner made a final rejection to pending Claims 28-32 and 44-52. A Notice of Appeal was filed on July 15, 2005, and Appellants' Appeal Brief was filed September 12, 2005.

An Examiner's Answer was mailed on December 2, 2005. The following constitutes Appellants' Reply Brief in response to the Examiner's Answer. This Reply Brief is accompanied by a Request for Oral Hearing.

ARGUMENTS

Claim Rejections Under 35 U.S.C. §112, Written Description

Claims 28-32 and 44-52 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description for the recited variant nucleic acids encoding polypeptides having at least 80% amino acid sequence identity to SEQ ID NO:220, wherein the polypeptide induces proliferation of kidney mesangial cells, or wherein the polypeptide induces proliferation of pancreatic β-cell precursor cells. The Examiner cites the following arguments in support of the rejection:

(1) the U.S.P.T.O.'s Written Description Guidelines require a structure-function relationship which is not found in the instant claims or the supporting specification;

(2) the instant claims are distinct from those provided as an example of adequately described nucleic acid variants in Example 9 of the Written Description Guidelines;

(3) the specification fails to provide a representative number of species to describe the claimed genus;

(4) the claimed genus broadly encompasses species other than human; and

(5) the instant claims are comparable to those found to lack written description in *Rochester*.

The Examiner's arguments will be addressed in the order they are listed above.

Central to the Examiner's argument is the assertion that the claims lack adequate written description because the definition of the claimed nucleic acids "lacks the correlation between structure and function that is at the heart of the caselaw and of the written description guidelines." (Page 5 of the Examiner's Answer). The U.S.P.T.O. Written Description Guidelines, however, do not require a structure-function relationship. The Written Description Guidelines, at page 8, note five factors provided for analysis for compliance with the written description guidelines: a) partial structure; b) physical and/or chemical properties; c) functional characteristics; d) known or disclosed correlation between structure and function; e) method of making; and f) combinations of any of these factors. A structure-function correlation is only one possible factor. A combination of other factors, such as partial structure, functional

characteristics, and method of making, all of which are disclosed for the instantly claimed variants, is also sufficient to provide written description.

Furthermore, Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office clearly states that protein variants meet the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins are routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity and a defined degree of sequence identity to the reference sequence. The instant claims are in the format exemplified by Example 14. As discussed in Appellants' Brief, the procedures for making the claimed nucleic acids encoding variant proteins are well known in the art and described in the specification. The specification also provides assays, shown in Example 145 and Example 151, for detecting the functional activity of the recited polypeptide variants. Finally, the recited variant proteins possess both the specified functional activity and a defined degree of sequence identity to the reference sequence, SEQ ID NO:220. Accordingly, the claimed variants meet the standards set forth in the Written Description Guidelines and exemplified by Example 14.

The Examiner's Answer asserts that the analysis in the Written Description Guidelines is "based upon the assumption that there will be insubstantial variation." (Pages 8-9 of the Examiner's Answer). The Examiner asserts that in Example 9 "the argument of insubstantial variation was that there was an expectation that stringently hybridizing proteins which retained the specific function of stimulating adenylate cyclase would differ insubstantially." (Page 9 of the Examiner's Answer).

Appellants respectfully point out that Example 9 describes nucleic acids which hybridize under stringent conditions to a reference sequence. In this case the functional limitation of hybridization can also be construed as a structural limitation, as another way of stating that the claimed sequence must have a certain degree of sequence homology to a reference sequence. In the instant case, however, structural limitations are already present in the claims, in the recitation

of at least 80% identity to SEQ ID NO:220, and need not be indirectly deduced from a functional recitation. In the instant case the functional limitation supplements the recited structural limitations rather than substituting for them.

Appellants further note that the encoded protein of Example 9 does not have adenylate cyclase activity, but binds to a dopamine receptor and stimulates adenylate cyclase activity. Thus, contrary to the Examiner's assertion, there is no "requirement of Example 9 for a structure function relationship." (Page 12 of the Examiner's Answer). The function of the protein of Example 9 in stimulating adenylate cyclase activity provides no further information about the structure of this protein than the function of PRO1382 in inducing proliferation of kidney mesangial cells and pancreatic β-cell precursor cells provides about the structure of PRO1382.

Of equal relevance to the instant claims although not discussed in the Examiner's Answer, Example 14 states that the claimed protein was isolated from liver and found to catalyze a certain reaction. This is parallel to the instant case in which PRO1382 was isolated and found to induce proliferation of kidney mesangial cells and pancreatic β-cell precursor cells. There is no indication in Example 14 that the specification provided any description of particular sequences required for enzymatic activity. Thus the functional limitation of Example 14 is comparable to that in the instant claims - both clearly limit the structure of the variants in the obvious sense that a protein lacking any structural similarity with the reference sequence would not be expected to conserve the same function. Appellants recognize that there may be polypeptides that induce proliferation of kidney mesangial cells or pancreatic β-cell precursor cells through mechanisms unrelated to those of PRO1382, and thus do not resemble PRO1382 in structure. These structurally unrelated polypeptides, however, would not be encompassed by claims that also require at least 80% amino acid sequence identity to SEQ ID NO:220. Appellants claim only those proteins which meet both limitations of the claims, structural and functional. Given the structural limitation, the additional functional limitation clearly acts to further define the claimed genus, as it does in Example 14.

Example 14 states that the specification "indicates that procedures for making proteins with substitutions, deletions, insertions and additions are routine in the art and provides an assay

for detecting the catalytic activity of the protein." As discussed in Appellants' Brief, the specification provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity, including a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids. This is the precisely the same type and level of guidance as described in Example 14. Accordingly, the instant claims are comparable to those in Example 14, and meet the written description guidelines.

The Examiner's Answer next discusses the alleged "absence of a representative number of species" at pages 7-8. The Examiner's assertion that the claimed genus of nucleic acids includes 4^{120} sequences is incorrect, because the claimed genus includes only those nucleic acids encoding polypeptide variants having at least 80% identity to SEQ ID NO:220 which also have a specified activity, that is, inducing proliferation of kidney mesangial cells, or inducing proliferation of pancreatic β-cell precursor cells. Once the additional functional limitations are included, the genus is limited to a size where the demonstrated species suffices to represent the genus.

The Examiner's Answer next asserts that Appellants' claims suffer from the same flaw as in *Lilly*, since the instant claims would allegedly encompass sequences from other species. The issue is not whether the claims encompass sequences from other species, but whether the claimed sequences are adequately described. The assumption that any claim which covers sequences from another species is automatically too broad would lead to the perverse result that a genus that was more highly conserved across species would be harder to provide written description for, since any given degree of sequence identity would be more likely to include the variants from other species. The Examiner asserts that "this would be the desired result" as indicated by the Federal Circuit's decision in *Lilly*. Appellants respectfully submit that the decision in *Lilly* was not based upon the fact that the claims encompassed sequences from more than one species, but upon the determination that the sequence from only one species had been described, with the claimed human insulin cDNA described only by its desired function. Nothing in *Lilly* contradicts Appellants' position that a genus of nucleic acid sequences may be described by a combination of structural and functional features, and that this genus may include sequences from more than one species.

Finally, the Examiner's Answer asserts that the recent case of *University of Rochester v. G.D. Searle & Co., Inc.* supports the instant rejection. (Page 12 of the Examiner's Answer). The case of *Rochester* is not parallel to the instant situation, as *Rochester* concerns a situation in which functional limitations alone, without any structural limitations, were ruled insufficient to provide adequate written description. In *Rochester*, the claims were to inhibitor compounds. The protein to be inhibited was described, and a specific assay for screening compounds including peptides, polynucleotides, and small organic molecules for inhibitory activity was provided, but not a single example of an inhibitor was provided. Thus the recited functional limitation did not provide sufficient guidance as to which of the vast universe of peptides, polynucleotides and small organic molecules might possibly have inhibitory activity. While the instant claims also have a structural limitation, in that the claimed variants must have at least 80% sequence identity to the reference sequence of SEQ ID NO:220, the claims in *Rochester* were limited solely by the function of the desired compound.

Thus *Rochester* does not demonstrate, as the PTO attempts to argue, that there must be a structure-function correlation. What *Rochester* shows is that absent any structural limitations, a functional limitation alone does not suffice. This analysis is not relevant to the instant case, in which structural limitations are already present in the claims and need not be indirectly deduced from a functional recitation. In the instant case the functional limitation supplements the recited structural limitations rather than substituting for them.

As discussed above, the claimed sequences are defined both by a structural limitation (encoding proteins having at least 80% amino acid sequence identity to a described reference sequence), and by a functional limitation, (encoding proteins having a specific biological activity, as measured by specific, disclosed assays). The specification also discloses methods of making the recited nucleic acids encoding polypeptide variants. The instant claims and specification thus include all of the factors accepted in Example 14 of the Written Description Guidelines as sufficient to provide written description for a claimed genus of sequences. Accordingly, the recited biological activity, coupled with a well defined, and relatively high degree of sequence identity, sufficiently defines the claimed genus such that one skilled in the art would readily

recognize that the Appellants were in the possession of the invention claimed at the effective filing date of this application.

CONCLUSION

For the reasons given above, Appellants submit that Claims 28-32 and 44-52 meet the written description requirement of 35 U.S.C. §112, first paragraph.

Accordingly, reversal of the rejection of claims 28-32 and 44-52 under 35 § U.S.C. 112, first paragraph, is respectfully requested.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C54**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: February 1, 2006

By: _____
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